Relationship between venous pressure and tissue volume during venous congestion plethysmography in man

F. Christ, J. Gamble*, H. Baschnegger and I. B. Gartside*

*Institute of Anaesthesiology, Ludwig–Maximilians University Munich, Marchioninistrasse 15, Munich, 81377 Germany and *Department of Physiology, Charing Cross and Westminster Medical School, Duncstan Road, London, W5 8RT, UK*

1. Venous congestion strain-gauge plethysmography enables the non-invasive assessment of arterial blood flow, fluid filtration capacity (K_f), venous pressure (P_v) and isovolumetric venous pressure (P_{vi}) in man. One of the major assumptions of this technique, that cuff pressure (P_{cuff}) applied to the limb equals P_v at the level of the strain gauge, was tested in this study.

2. In nine healthy male volunteers (mean age, 29·3 ± 1·2 years) the saphenous vein was cannulated with an 18-gauge catheter proximal to the medial malleolus. The subjects were supine and P_v was continuously measured during the application of small step (8–10 mmHg) increases in congestion P_{cuff} (up to 70 mmHg). P_{cuff}, changes in limb circumference and P_v were recorded by computer for off-line analysis. Since the determination of K_f is influenced by the changes in plasma oncotic pressure, venous blood samples were obtained at the start of the study, when P_{cuff} was raised to 30 mmHg and again to 65 mmHg and 4 min after deflation of the cuff.

3. The relationship between P_v and P_{cuff} was linear over the range of 10–70 mmHg ($n = 9$, 69 measurements, slope 0·91, $r = 0·97$, $P \ll 0·001$). The non-invasively measured calf P_v, based on the intercept of the relationship between the vascular compliance component (V_a) and P_{cuff}, was 8·0 ± 0·4 mmHg, which was not significantly different from the corrected invasively measured P_v value of 8·8 ± 0·3 mmHg ($P = 0·08$).

4. Venous blood lactate and haemoglobin concentrations, as well as colloid osmotic pressure, total protein and albumin concentrations were unchanged throughout the protocol, whereas significant decreases in P_{O_2} and blood glucose concentration were observed when P_{cuff} reached 65 mmHg. Assuming a constant oxygen consumption, this may suggest a reduction in tissue perfusion.

5. This study demonstrates the close correlation between P_{cuff} and P_v in the saphenous vein. Since the small congestion P_{cuff} step protocol does not cause significant increase in plasma oncotic pressure, we conclude that P_v, as well as K_f, can be accurately determined with this venous congestion plethysmography protocol.

Venous congestion strain-gauge plethysmography (VCP) was first introduced by Whitney for the non-invasive assessment of arterial blood flow in man (Whitney, 1953). This method also enables the non-invasive determination of fluid filtration capacity (K_f), venous pressure (P_v) and isovolumetric venous pressure (P_{vi}), the cuff pressure which has to be exceeded to induce net fluid filtration (Mellander, Öberg & Odelram, 1964; Michel & Moyses, 1987). We recently described a modified computer-assisted strain-gauge plethysmography protocol using small venous congestion pressure steps (Gamble, Gartside & Christ, 1993). When venous congestion cuff pressure (P_{cuff}) exceeds the ambient filtration pressure, a change in limb volume is observed, which reflects two processes. The first process, a rapid volume change, is attributable to venous filling as the pressure rises. The second process, a slower and sustained component, occurs when the raised microvascular hydrostatic force exceeds the oncotic force and is attributed to fluid filtration in the microvasculature. K_f is determined from the relationship between fluid filtration and the applied P_{cuff} (Gamble *et al.* 1993). None of these processes will occur until the congestion P_{cuff} exceeds the ambient P_v, so that the first sign of a volume response will indicate that the ambient P_v has been exceeded.

One objective of the present paper was to make direct, invasive assessments of the relationship between congestion P_{cuff}, P_v and the resulting limb volume response, in order to validate the assumptions of our non-invasive protocol,

i.e. that the applied congestion P_{cuff} reflects the P_v distal to the congestion cuff (Gamble *et al.* 1993). In a previous paper we showed that the subcutaneous and intramuscular interstitial fluid pressure does not change following small step increases in P_v (Christ, Dellian, Goetz, Gamble & Messmer, 1997). Other Starling forces may be altered by the elevation of local P_v. For instance, enhanced fluid filtration will induce an increase in local haematocrit and in plasma oncotic pressure (Youmans, Wells, Donley, Miller & Frank, 1934; Noddeland, Aukland & Nicolysen, 1981; Aukland & Reed, 1993; Rayman, Williams, Gamble & Tooke, 1994). Such a change may be predicted in situations where the nutritional blood flow is low, especially when this coincides with increased microvascular permeability, for instance in shock states (Aukland & Reed, 1993). The resulting increase in fractional extraction of plasma water would alter the plasma protein concentration at the microvascular interface and thus limit fluid filtration (Aukland & Reed, 1993). Such changes in Starling forces would influence the determination of K_f with venous congestion plethysmography. In the current study we measured plasma oncotic pressure and haematocrit in samples of venous blood draining from the foot.

Recently we used near-infrared spectroscopy (Brazy, 1991) and showed that there was no evidence of impaired skeletal muscle tissue perfusion during the study protocol adopted by Christ *et al.* (1997). In the present study we extend these observations by measuring the changes in blood lactate and glucose concentrations and in the blood gases of venous blood samples collected from cannulae advanced close to the site of the strain gauge, during the course of the protocol.

METHODS

All subjects gave their written, informed consent and the study was approved by the local ethical committee.

Venous congestion plethysmography (VCP)

Since the venous congestion strain-gauge plethysmography apparatus and protocol have been described in detail elsewhere (Gamble *et al.* 1993), we will only give an outline of the basic protocol used in the present study. Nine healthy male subjects (mean age, 29·3 ± 1·2 years) were studied. Before the subject lay down, a sterile 18-gauge cannula (Abbocath; length, 4·5 cm; Abbott, Wiesbaden, Germany) was inserted into the saphenous vein of one leg, just proximal of the medial malleoulus and then advanced to its maximum length. The cannula was flushed with sterile heparinized normal saline (0·9% NaCl) and connected to a Statham transducer (Spectramed, Watford, UK). After venous cannulation, the subjects lay supine for at least 20 min prior to the commencement of the study protocol. The legs were supported on a vacuum mattress with the mid-calf levelled with respect to the right atrium (one-third of the distance from sternal angle to the surface of the supporting bench). Congestion cuffs were fitted bilaterally at mid-thigh level and connected to an air pump via a variable resistance, which enabled increases in P_v to be applied to the thighs. P_{cuff} was measured using the in-built pressure-recording device (Gamble *et al.* 1993). The circumference of each calf was measured before the strain gauge was attached. The gauges were set to a standard tension and calibrated at the start of each study.

Measurement of P_v

The cannula was periodically flushed with sterile heparinized NaCl, always at least 1 min before the imposition of a new P_{cuff} step. P_v was recorded continuously with a Siemens 300 series monitor and the signal fed via an A/D converter card (Amplicon PC30, Brighton, UK) into one of the external channels of the VCP computer. This enabled the simultaneous and continuous recording of P_{cuff} and P_v, together with the strain-gauge signals from both limbs. The P_v reading was taken at least 120 s after P_{cuff} elevation; Brown *et al.* (1966) have shown that this time may be required to achieve a value representing the P_v of the whole extremity at the level of the cannula.

Blood samples

Venous blood samples were obtained at the start of the study (stage 1), then just before the subsequent pressure changes to 30 mmHg (stage 2) and 65 mmHg (stage 3), respectively, and finally 4 min after deflation of the congestion cuff (stage 4). We used the samples for measurement of blood glucose and lactate concentrations (lactate analyser, YSI 2300 Stat, Yellow Springs Instruments, Yellow Springs, OH, USA), as well as osmolality (Micro Osmometer 3MO, Advanced Instruments, Needham Height, MA, USA). Blood gas analyses were also performed (Radiometer ABL 520, Copenhagen, Denmark). Colloid osmotic pressure was determined with a membrane osmometer (Onkometer, 2ONC Berlin, Germany) fitted with a membrane which had a 'cut-off' of 20 000 Da (Onkometer, 2ONC Berlin, Germany), and albumin and total protein concentrations were measured using standard techniques.

Protocol

Cumulative congestion pressure steps were each of 5 min duration and 8–12 mmHg in size. The final pressure used did not exceed the diastolic blood pressure, which was measured in each subject at the start of the study. After the maximum pressure step had been achieved, the cuff congestion was released and, after a 4 min recovery period, the data were saved to disk for off-line analysis. The difference in vertical height between the locations of the venous cannulation site, with respect to the mid-point of the thigh under the congestion cuff and the mid-point of the calf at the site of the strain gauge, were measured so that the appropriate height related pressure corrections could be made. The vertical height, in centimetres, was corrected to millimetres of Hg using the factor 0·766, which includes a correction for the specific gravity of blood, which was assumed to be 1·055.

Analysis

Full details of the analysis procedure have been published previously (Gamble *et al.* 1993). The elevation of P_{cuff} above the existing P_v causes a rapid increase in limb volume attributable to venous filling. With the small cumulative pressure step sizes used in this study, the venous filling component was completed within 90 s (Gamble *et al.* 1993). When the congestion pressure was sufficient to exceed the initial steady-state balance of Starling forces, a sustained increase in volume, attributable to fluid filtration into the tissue, was also observed. In the analysis system used, the fluid filtration rate (J_v) was determined by least-squares regression and subtracted from the total volume response to the pressure increment. The residual volume change, due to venous filling, was then subjected to exponential analysis, enabling the size of the volume change to be determined (V_a) (Gamble *et al.* 1993). The relationship between P_{cuff} and V_a is curvilinear and the intercept with the x-axis, obtained by extrapolation using a non-linear fitting routine (Sigma Plot, Jandel Scientific), should represent P_v at the level of the strain gauge (Gamble *et al.* 1993). Comparison

Table 1. Comparison of results obtained from the different protocols

Subject	P_v VCP (mmHg)	P_v invasive (mmHg)	P_{vl} (mmHg)	K_f (10^{-3} ml mmHg^{-1} (100 ml tissue)$^{-1}$)
J.B.	8·1	9·0	17·5	4·9
M.N.	7·1	9·1	25·0	5·6
F.C.	8·4	9·4	14·0	4·3
P.R.	10·0	9·0	13·0	5·8
C.M.	7·1	8·5	34·6	8·1
K.M.	8·7	8·2	27·5	4·9
M.I.	7·0	10·0	22·1	9·1
C.S.	9·0	9·0	20·9	6·7
H.B.	6·5	7·0	33·6	7·8
Mean	8·0 ± 0·4	8·8 ± 0·3	22·5 ± 2·0	6·2 ± 0·5

The individual P_v values obtained from the venous congestion plethysmography protocol (P_v VCP) and those values measured with an indwelling venous cannula (P_v invasive) as well as the isovolumetric venous pressure (P_{vl}) and the fluid filtration capacity (K_f) are given. The means ± S.E.M. are also given.

between invasively measured P_v and values deduced from the plethysmography study were made using these data.

Statistical analysis

Invasively obtained and plethysmographically determined P_v were compared using Student's paired t test. The remaining data were analysed using paired one-way ANOVA for repeated measurements. The data are given as mean values ± S.E.M. Significance was assumed when $P < 0·05$.

RESULTS

No complications resulted from either the non-invasive or invasive measurements performed in these studies. Sixty-nine measurements of P_{cuff} and P_v from nine subjects could be summarized by the relationship between P_v and P_{cuff}, which was linear over the range of 10–70 mmHg and had the equation $y = 0·91x + 2·5$ ($r = 0·97$, $P \ll 0·001$, Fig. 1).

Since P_{cuff} at the start of the study was 0 mmHg and the ambient P_v at the level of the cuff had to be greater than 0 mmHg, we corrected the invasively measured P_v value for the resulting hydrostatic pressure difference in each subject. The mean venous cannulation site was 6·9 ± 0·5 cm higher than the mid-calf and 8·8 ± 0·8 cm higher than mid-cuff. The resulting calf P_v based on the intercept of the relationship between V_a and P_{cuff} was 8·0 ± 0·4 mmHg, which was not significantly different from the corrected invasive P_v value of 8·8 ± 0·3 mmHg ($P = 0·08$). Table 1 shows the P_v values obtained from the VCP protocol and the invasively measured values (P_v invasive) as well as P_{vl} and the fluid filtration capacity of each individual investigated.

Throughout the elevation of P_v the venous blood samples revealed no significant changes in colloid osmotic pressure,

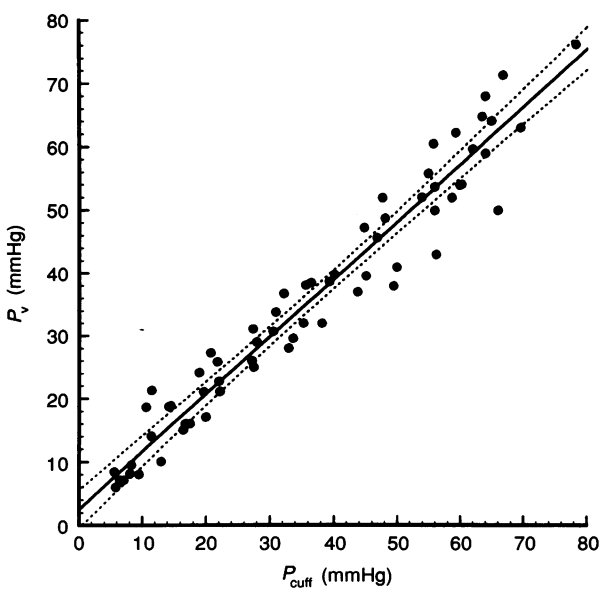

Figure 1

The relationship between the measured P_v and the applied P_{cuff} for all subjects (69 measurements in 9 subjects) is shown. The continuous line represents the linear regression, which could be described as $y = 0·91x + 2·5$ with a regression coefficient of $r = 0·97$. The dotted lines are the 99% confidence intervals.

Table 2. Results from venous blood samples

	Stage 1	Stage 2	Stage 3	Stage 4
[Protein] (g dl^{-1})	6·0 ± 0·6	6·5 ± 0·5	6·5 ± 1·4	6·4 ± 0·6
[Albumin] (g dl^{-1})	5·1 ± 0·5	5·4 ± 0·5	5·0 ± 0·9	5·1 ± 0·2
COP (mmHg)	21·8 ± 4·1	24·1 ± 3·9	21·1 ± 4·4	23·3 ± 2·5
[Lactate] (mmol l^{-1})	1·1 ± 0·2	1·1 ± 0·2	1·1 ± 0·3	1·0 ± 0·2
[Glucose] (mg (100 ml)$^{-1}$)	89·7 ± 9·2	81·7 ± 8·8	71·1 ± 14·4*	79·5 ± 8·0
Osmolality (mosmol kg^{-1})	292·0 ± 6·7	289·5 ± 4·9	295·2 ± 9·7	286·3 ± 2·6
[Hb] (g dl^{-1})	14·1 ± 0·8	13·8 ± 1·4	13·1 ± 1·6	14·3 ± 0·5
HbO_2 (%)	71·5 ± 13·2	60·7 ± 15·5	44·5 ± 13·1*	57·7 ± 14·6*
O_2 saturation (%)	72·3 ± 13·6	61·4 ± 15·8	44·8 ± 13·0*	63·4 ± 15·6
P_{O_2} (mmHg)	42·7 ± 10·4	35·5 ± 8·12	28·1 ± 5·3*	36·8 ± 8·5
P_{CO_2} (mmHg)	47·2 ± 5·1	47·2 ± 7·8	48·3 ± 3·3	48·8 ± 4·3
P_{50}	28·4 ± 1·4	28·9 ± 1·3	30·1 ± 1·5	28·9 ± 1·6
[HCO_3] (mmol l^{-1})	27·5 ± 1·0	26·5 ± 4·0	25·4 ± 1·7*	27·4 ± 1
BE (mmol l^{-1})	2·3 ± 0·8	1·0 ± 3·5	−0·3 ± 1·6*	1·6 ± 1·8
pH	7·38 ± 0·03	7·36 ± 0·03	7·34 ± 0·03*	7·37 ± 0·03

* $P < 0·05$. The results are summarized from blood samples collected from the saphenous vein during small step increases in venous congestion pressure, which were obtained at the start of the study (Stage 1), when P_{cuff} was raised to 30 mmHg (Stage 2) and 65 mmHg (Stage 3), respectively, and 4 min after deflation of the congestion cuff (Stage 4). [Protein], total protein content; COP, colloid osmotic pressure; [Hb], haemoglobin concentration; HbO_2, percentage oxygenated haemoglobin; BE, base excess.

albumin and total protein concentrations (Table 2). Moreover, the lactate and Hb concentrations and osmolality remained unchanged throughout the protocol, whereas significant decreases in P_{O_2} and blood glucose concentration were observed at stage 3 when the P_{cuff} was 65 mmHg.

The K_f value measured was 6·24 ± 0·53 × 10^{-3} ml $mmHg^{-1}$ (100 ml tissue)$^{-1}$ and P_{vi} was 22·45 ± 2·00 mmHg, both values were not significantly different from previously published data from our group (Christ *et al.* 1997; Table 1).

DISCUSSION

The data obtained in these studies show the close relationship between the applied congestion P_{cuff} and the P_v measured in the saphenous vein close to the strain gauge. These data support our contention that the VCP protocol enables the accurate assessment of K_f and P_{vi}, when small cumulative congestion P_{cuff} steps are used. Since the cannula was inserted into a superficial vein it might be argued that the measured pressure may not reflect the P_v in the deeper veins, which drain most of the blood from the lower limb. The latter point is corroborated by the observations of Buckey, Peshock & Blomqvist, (1988) who, using magnetic resonance imaging, reported that at 40 mmHg of venous congestion pressure, 90·2% of the vascular volume of the calf can be attributed to deep venous filling. Moreover, Sejrsen, Henriksen, Paaske & Nielsen, (1981) using a xenon-washout technique found that periods of 3, 4 and 5 min were required to achieve steady state after venous congestion pressure steps of 20, 30 and 40 mmHg, respectively, suggesting that this amount of time was required to achieve a constant vascular volume. Brown, Greenfield, Goei & Plassaras (1966) found that limb P_v required 120 s to equilibrate after the imposition of a venous congestion pressure step. If one allows for this time span, then the value obtained for different venous cannulation sites varied by only 1–2 mmHg (Brown *et al.* 1966). Furthermore, it has been shown that the pressure gradient between the deep and the superficial veins is small, because the venous blood usually drains through low resistance valves (Brown *et al.* 1966). We applied pressure steps < 12 mmHg and we always measured P_v after at least 120 s following the imposition of the pressure step, which was sufficient time to achieve a new stable value in each case. In the light of the above mentioned observations we believe that the values given here represent a good estimate of superficial and deep P_v.

Discussion of the blood sample data

Youmans *et al.* (1934), Noddeland *et al.* (1981) and Rayman *et al.* (1994) reported an increase in plasma oncotic pressure of venous blood draining from the foot during dependency. This was explained by the activation of the veno-arterial 'reflex' and the enhanced fluid filtration in the dependent limb (Gamble, Gartside & Christ, 1997). We did not observe any significant changes in plasma oncotic pressure of venous blood during the small step VCP protocol. The difference is probably explained by the failure of small cumulative

increases in P_v to activate the veno-arterial 'reflex'. However, the results on the blood composition have to be viewed with caution, since the blood was drawn from a superficial vein, which may not reflect the oncotic pressures and the haematocrit at the microvascular interface at which K_f is determined.

No significant increase in blood lactate concentration was observed during venous congestion plethysmography. This indicates that tissue oxygenation is not impaired during this protocol, and corroborates our results from a previous study using near-infrared spectroscopy, where we have shown that tissue HbO_2 and cytochrome aa3 concentration, which we used as an index of tissue oxidative function, remain unchanged (Christ *et al.* 1997). Moreover, impaired tissue perfusion seems unlikely since during standing similar P_v values may be continually experienced in the limb, without causing microvascular damage.

We previously reported, that skin blood flow assessed with laser Doppler fluid, is markedly reduced when venous congestion pressure is raised above 35 mmHg (Christ *et al.* 1997). Since the venous blood was collected from a superficial vein, which predominantly drains blood from the skin, we believe that the decrease in P_{O_2} is probably explained by the known reduction in skin blood flow in response to such challenges. However, if one assumes that oxygen consumption remained constant during the VCP protocol, then the decrease in P_{O_2} could also be explained by a reduction in the overall tissue perfusion.

In conclusion, this study provides valuable support for one of the assumptions of venous congestion strain-gauge plethysmography, by showing the close relationship between P_{cuff} applied at the thigh and the P_v measured in the saphenous vein. We found further evidence for the advantages of small pressure steps in the measurement of K_f and P_{vi}. Finally, we have also shown that venous congestion plethysmography enables the accurate non-invasive measurement of limb P_v.

AUKLAND, K. & REED, R. K. (1993). Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. *Physiological Reviews* **73**, 1–78.

BRAZY, J. E. (1991). Skeletal muscle oxygenation monitoring by near infrared spectroscopy. *Biochemistry International* **25**, 241–248.

BROWN, E., GREENFIELD, A. D., GOEI, J. S. & PLASSARAS, G. (1966). Filling and emptying the low pressure blood vessels of the human forearm. *Journal of Applied Physiology* **21**, 573–582.

BUCKEY, J. C., PESHOCK, R. M. & BLOMQVIST, C. G. (1988). Deep venous contribution to hydrostatic blood volume change in the human leg. *American Journal of Cardiology* **62**, 449–453.

CHRIST, F., DELLIAN, M., GOETZ, A. E., GAMBLE, J. & MESSMER, M. (1997). Changes in subcutaneous interstitial fluid pressure, tissue oxygenation and skin red cell flux during venous congestion plethysmography in man. *Microcirculation* **4**, 75–81.

GAMBLE, J., GARTSIDE, I. B. & CHRIST, F. (1993). A reassessment of mercury in silastic strain gauge plethysmography for the microvascular permeability assessment in man. *Journal of Physiology* **464**, 407–422.

GAMBLE, J., GARTSIDE, I. B. & CHRIST, F. (1997). The effect of passive tilting on microvascular parameters in the human calf; a strain gauge venous occlusion plethysmography study. *Journal of Physiology* **498**, 541–552.

MELLANDER, S., ÖBERG, B. & ODELRAM, H. (1964). Vascular adjustments to increased transmural pressure in cat and man with special reference to shifts in capillary fluid transfer. *Acta Physiologica Scandinavica* **61**, 34–48.

MICHEL, C. C. & MOYSES, C. (1987). The measurement of fluid filtration in human limbs. In *Clinical Investigations of Microcirculation*, ed. TOOKE, J. E. & SMAJE, L. H., pp. 103–126. Morhuis Nyhoff, Boston.

NODDELAND, H., AUKLAND, K. & NICOLAYSEN, G. (1981). Plasma colloid osmotic pressure in venous blood from the human foot in orthostasis. *Acta Physiologica Scandinavica* **113**, 447–454.

RAYMAN, G., WILLIAMS, S. A., GAMBLE, J. & TOOKE, J. E. (1994). A study of factors governing fluid filtration in the diabetic foot. *European Journal of Clinical Investigation* **24**, 830–836.

SEJRSEN, P., HENRIKSEN, O., PAASKE, W. P. & NIELSEN, S. L. (1981). Duration of increase in vascular volume during venous stasis. *Acta Physiologica Scandinavica* **111**, 293–298.

WHITNEY, R. J. (1953). The measurement of volume changes in human limbs. *Journal of Physiology* **121**, 1–27.

YOUMANS, J. B., WELLS, H. S., DONLEY, D., MILLER, D. G. & FRANK, H. (1934). The effect of posture (standing) on the serum protein concentration and colloid osmotic pressure of blood from the foot in the relation to the formation of oedema. *Journal of Clinical Investigation* **13**, 447–459.

Acknowledgements

The authors would like to thank Christian Mosev, Markus Niklas and Patrik Raithil for helping to collect the data.

Author's email address

F. Christ: Frank.Christ@ana.med.uni-muenchen.de

Recieved 20 January 1997; accepted 16 May 1997.